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(54) Title: INHIBITION OF HAIR GROWTH (57) Abstract Mammalian hair growth is cosmetically reduced by applying to the skin a composition including pantothenic acid or an analogue of pantothenic acid.		

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INHIBITION OF HAIR GROWTH

This invention relates to inhibition of mammalian hair growth for cosmetic purposes.

U.S. Pat. No. 4,039,669 describes the
5 topical use of 17-alpha-R-androst-4-en-17-beta-
ol-3-one or esters thereof where the R is n-
propyl or n-butyl for the control of
dermatological systems associated with androgen-
mediated conditions such as acne.

10 U.S. Pat. Nos. 4,139,638 and 4,161,540
describe the use of certain 4'-substituted and
3',4'-disubstituted anilides for the treatment
of androgen-dependent disease states such as
female hirsutism and acne.

15 U.S. Pat. No. 4,191,775 discloses that
certain 3,4-disubstituted branched-chain
fluorinated acylanilides may be used in the
topical treatment of androgen-dependent disease
conditions such as acne, female hirsutism, and
20 seborrhea.

U.S. Pat. No. 4,344,941, describes the
topical use of certain androgenic 17-alpha-
substituted steroids exemplified by 17-beta-
hydroxyl-1-alpha-methyl-17-alpha(1-methyl-2-
25 propenyl)-5-alpha-androstan-3-one for the
treatment of diseases such as acne, seborrhea,
alopecia and female hirsutism.

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West German OLS 2,840,144 describes the use of a combination of progesterone with either cyproterone acetate or chlormadinone acetate in the topical treatment of androgen induced hormonal disturbances such as alopecia, female hirsutism, and acne.

20 Another process for extending the
duration of depilation is described in U.S. Pat.
No. 4,370,315. The process therein comprises
the topical application of a composition
25 containing a lipooxygenase along with linoleic
acid or derivative thereof. The patent
describes the application of such composition to
various body parts of female human subjects in
the majority of which regrowth of hair was
clearly perceptible only after six or more
30 weeks.

In U.S. Pat. No. 4,439,432 topical compositions containing progesterone are reported for use in treatment of progesterone deficiency and related conditions, including abnormal hair growth resulting from androgen excess. Further insights on this point may be obtained from the related literature, among

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which mention may be made of Simpson et al.

"The Effect of Topically Applied Progesterone on Sebum Excretion Rate," Br. J. Derm., Vol. 100, p. 687 (1979), in which progesterone was

5 reported effective in reducing sebum excretion rates in females, but without effect in males. In Goos et al., "An Improved Method for

Evaluating Antiandrogens," Arch. Dermatol. Res. vol. 273, pp. 333-341 (1982), the effect of

10 progesterone on inhibition of hair growth in intact males appears to be doubtful (p. 340, Table 3, Group VI vs. Group X). In Burdick et al., "The Topical Effect of the Antiandrogen

15 Chloromadinone Acetate and Some of Its Chemical Modifications on the Hamster Costovertebral Organ," Br. J. Derm., Vol. 82, Supplement 6, p. 19 (1970), antiandrogens were either ineffective or of questionable effect in inhibiting flank organ function in normal intact male hamsters.

20 Similarly, in Girard et al., "Inhibition of Testosterone Metabolism and Lipogenesis in Animal Sebaceous Glands by Progesterone," Arch. Dermatol. Res., Vol. 269, pp. 281-290 (1980), progesterone is found effective in the female

25 but not in the male. In all of the above experiments topical antiandrogens were ineffective in males in inhibiting androgenic function. When the female and male responses were compared in both humans and hamsters, only

30 females responded to topical treatment.

In U.S. Pat. No. 4,269,831 a substantial reduction in hair growth of the hamster flank organ is among the effects reported from topical application of 17β -

35 hydroxy- 17α -propylandroster-4-en-3-one. However reduction in the size of the flank organ is also described, leaving a smaller field on which the

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hair can grow. Therefore, the reduction in hair growth may be a consequence of a decrease in area of the flank organ rather than an alteration in the character of the hair.

5 U.S. Pat. No. 4,885,289 describes altering the rate and character hair growth by topical application of 5-alpha-reductase inhibitors and/or cytoplasmic androgen receptor
10 describes the topical application of ornithine decarboxylase inhibitors for similar purposes, either alone or in combination with the materials of U.S. Pat. No. 4,885,289. U.S. Pat. No. 5,095,007 describes inhibiting hair growth
15 by applying inhibitors of adenylosuccinate synthetase or aspartate transcarbamylase. U.S. Pat. No. 5,096,911 describes inhibiting mammalian hair growth by applying inhibitors of gamma-glutamyl transpeptidase. U.S. Pat. No.
20 5,132,293 describes inhibiting mammalian hair growth by applying inhibitors of 5-adenosylmethionine decarboxylase.

Pantothenic acid has been previously used in hair treatment methods. However,
25 previous methods have focused on the use of pantothenic acid as a hair moisturizer and stimulant of scalp hair growth. See, e.g., J. Am. College Toxicology 139 (1987) and Japanese Patent Publication No. 2,430,170.

30 It has now been found that mammalian (including human) hair growth can be cosmetically inhibited by applying to the skin a composition including pantothenic acid, or an analog of pantothenic acid, in an amount
35 effective to reduce hair growth in the applied area.

Pantothenic acid includes a carboxylic

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acid group that can be in either free (-COOH) or salt (-COOX, where X is a counterion) form. Accordingly, "pantothenic acid", as used herein, is meant to encompass both free and salt forms.

5 Analogues of pantothenic acid include derivatives, conjugates, and homologs of pantothenic acid, and salts thereof. Examples of derivatives of pantothenic acid include pantothenyl alcohol, calcium 4-
10 phosphonpantothenate, and 4'-amino-4'-deoxypantothenic acid; examples of conjugates of pantothenic acid include D-pantethine (a conjugate of pantothenic acid and cysteamine), pantetheine-S-sulfonate, 4-phospho-S-
15 benzoylpantetheine; and examples of homologs of pantothenic acid include hopantenate [calcium 4-(2,4-dihydroxy-3,3-dimethylbutyramido) butyrate hemihydrate].

 The cosmetic composition preferably
20 includes a non-toxic dermatologically acceptable vehicle or carrier which is adapted to be spread upon the skin. Examples of suitable vehicles are: a hydroalcoholic vehicle, cream, lotion or gel which can effectively deliver the active
25 compound to site of application. In addition, a penetration enhancer(s) may be added to the vehicle to further enhance the effectiveness of the formulation.

 The concentration of the inhibitor in
30 the composition may be varied over a wide range up to a saturated solution, preferably from 1 to 30% by weight or even more; the reduction of hair growth increases as the amount of inhibitor applied increases per unit area of skin. The
35 maximum amount effectively applied is limited only by the rate at which the inhibitor penetrates the skin. Generally, the effective

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amounts range from 100 to 3000 micrograms or more per square centimeter of skin.

The composition should be applied to the area of the body where it is desired to cosmetically inhibit hair growth. Typically, the composition can be applied to the face, particularly to the beard area of the face such as the cheek and chin. The composition can also be applied to the legs, arms, torso or armpit. In humans, the composition should be applied twice a day, or even more frequently, for at least three months to achieve a perceived reduction in hair growth.

Reduction of hair growth is demonstrated when the frequency of hair removal is reduced, or the subject perceives less hair on the treated site, or, quantitatively, when the weight of hair removed by shaving (i.e., hair mass) is reduced.

The following specific examples are intended to illustrate more clearly the nature of the present invention without acting as a limitation upon its scope.

Example 1

A vehicle or carrier was prepared having the following composition:

	<u>Component</u>	<u>Wt. Percent Concentration</u>
	Distilled Water	68%
	Ethanol (100 proof)	16%
30	Propylene glycol	5%
	Dipropylene glycol	5%
	Benzyl alcohol	4%
	Propylene carbonate	2%

Pantothenic acid hemicalcium salt (PTA) was mixed with separate portions of the foregoing vehicle to provide specimens containing 5, 10, 20, and 30% by weight, respectively, the pH of these formulations was in the range of pH 7-8.

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A group of male intact Golden Syrian hamsters was provided. These animals were considered acceptable models for human beard hair growth in that they display oval shaped flank organs, one on each side, each about 8 mm. in major diameter, which grow thick black and coarse hair similar to human beard hair. These organs produce hair in response to androgens in the hamster. The flank organs of each hamster were depilated by applying a thioglycolate based chemical depilatory (Surgex), and to one organ of each animal was applied 10-25 μ l. of vehicle alone once a day, while to the other organ of each animal was applied an equal amount of vehicle containing the analog. After thirteen applications (one application per day for five days a week), the flank organs were shaved and the amount of recovered hair (hair mass) from each was weighed. Percent-reduction of hair growth was calculated by subtracting the hair mass (mg) value of the test compound treated side from the hair mass value of the vehicle treated side; the delta value obtained was then divided by the hair mass value of the vehicle treated side, and the resultant number was multiplied by 100. The results were as shown in Table 1.

Example 2

D-Pantothenic acid monosodium salt (PTAss) was mixed with separate portions of the vehicle of Example 1 to provide specimens containing 5, 10, 20, and 30% by weight, respectively, of the analog and the pH of these formulations was in the range of pH 7-8.

A group of male intact Golden Syrian hamsters was treated as in Example 1, and percent inhibition was determined. The results

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were as shown in Table 1.

Example 3

Pantoyl alcohol (PTYA) was mixed with separate portions of the vehicle of Example 1 to provide specimens containing 5, 10, 20, and 30% by weight, respectively, of the analog and the pH was in the range of pH 7-8.

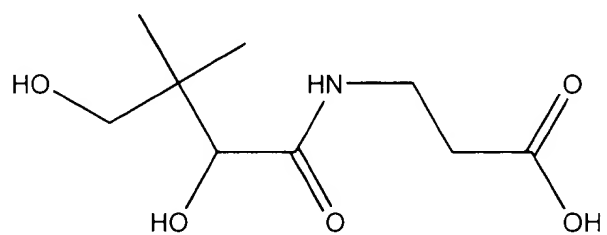
Two groups of male intact Golden Syrian hamsters were treated as in Example 1, and percent inhibition was determined. The results were as shown in Table 1.

Example 4

As a comparison to a known inhibitor of hair growth, described in U.S. Pat. No. 4,720,480 one group of eight animals was treated with a composition containing 10% DFMO (α -difluoromethyl ornithine) in the vehicle of Example 1; the pH of this formulation was 4.0. The treatments were as described in Example 1. The results were as shown in Table 1.

Example 5

As a control, one group of eight animals had both flank organs of each animal treated with vehicle alone. The results were as shown in Table 1.



pantothenic acid